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EDITORIAL COMMENTARY

One step closer to the elimination of primary graft dysfunction

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See related article on pages 596-602.

Primary graft dysfunction (PGD) is a significant cause of morbidity and mortality after lung transplants. As supported by the findings in the study published by Cantu and colleagues¹ in this issue of the *Journal*, as many as 30% of patients will have development of grade 3 PGD, defined by a Pao₂ to inspired oxygen fraction ratio less than 200 along with diffuse allograft infiltrates on chest radiography. Implicated in PGD is ischemia-reperfusion injury, which our laboratory has studied and published on extensively, as well as activation of the oxidant stress pathway. Although studies have shown that genetic variations alter the risk of acute lung injury, there are few data on human subjects describing the genes responsible for PGD after lung transplants. This article examines genetic variations associated with PGD in both donors and recipients of transplanted lungs.

FIGURE 1. Lungs from a porcine donor without a beating heart undergoing rehabilitation with ex vivo lung perfusion.

Cantu and colleagues¹ completed a large, multicenter prospective cohort study of lung transplant donors and recipients selected from the Lung Transplant Outcomes Group. DNA samples from 1038 lung transplant recipients and 392 lung donors were analyzed for the presence of 49 oxidant stress genes with single-nucleotide polymorphism set analysis. The data demonstrated that *GPX1*, *NFE2L2*, *NOS3*, *GSTM2*, *NOX3*, *NOS1AP*, and *PONI* were associated with grade 3 PGD and

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should be targeted by future studies. Additionally, a donor–recipient association between *NOX3* and *NFE2L2* was identified. This correlates nicely with the group’s previous research showing that *NFE2L2* is associated with a higher likelihood of development of acute lung injury after trauma.

The identified oxidant stress genes should be further investigated and not interpreted at this time as causative of PGD. Further clinical investigations validating these findings are warranted. Additional genes may be important in regulating oxidant stress, and future analyses are necessary to develop an inclusive list of single-nucleotide polymorphisms involved in the pathophysiology of PGD. Modulation of the genes identified in this study with preclinical animal models will be invaluable in answering the question of causality.

The findings of this study are important to the fields of lung transplantation and ischemia–reperfusion injury because they set the framework for future research. Determining the effect of certain genetic variations within the oxidant stress pathway on PGD will bring us one step closer to elimination of this deadly complication. There is also evidence that acute lung injury predisposes toward bronchiolitis obliterans, which is the major cause of late mortality.

Our laboratory focuses on determining how to expand the donor lung pool in a consistent and reliable fashion, as well as how to prevent ischemia–reperfusion injury. Through the use of ex vivo lung perfusion and adenosine 2A receptor activation, we have successfully rehabilitated lungs from porcine donors without beating hearts (Figure 1). Others have successfully used this technology clinically to rehabilitate lungs as well. Further understanding the role of oxidant stress genes in the development of ischemia–reperfusion injury will open the door to rapid advancement of the current body of knowledge. Once we have determined how each genetic variation contributes to the detrimental effects of ischemia–reperfusion injury and PGD, we can preemptively target certain donor lungs and recipients with individualized treatment strategies. Combining preoperative genetic testing with the rehabilitation capabilities of ex vivo lung perfusion may allow us to eliminate PGD and improve the rate of successful lung transplantation.

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